Clinical crosstalk between microRNAs and gastric cancer (Review)

JING OUYANG[1], ZHIZHONG XIE[1], XIAOYONG LEI[1],
GUOTAO TANG[1], RUNLIANG GAN[2] and XIAOYAN YANG[1]

[1]Institute of Pharmacy and Pharmacology, University of South China; [2]Cancer Research Institute,
Hengyang Medical College, University of South China, Hengyang, Hunan 421001, P.R. China

Abstract. Globally, there were over 1 million new gastric cancer (GC) patients in 2018 and GC has become the sixth most common cancer worldwide. GC caused 783,000 deaths worldwide in 2018, making it the third most deadly cancer type. miRNAs are short (~22 nucleotides in length) non-coding RNA molecules, which can regulate gene expression passively at a post-transcriptional level. There are more and more in-depth studies on miRNAs. There are numerous conclusive evidences that there is an inseparable link between miRNAs and GC. miRNAs can affect the entire process of GC, including the oncogenesis, development, diagnosis, treatment and prognosis of GC. Although many miRNAs have been linked to GC, few can be applied to clinical practice. This review takes the clinical changes of GC as a clue and summarizes the miRNAs related to GC that have confirmed the mechanism of action in the past three years. Through in-depth study and understanding of the mechanism of those miRNAs, we predict their possible clinical uses, and suggest some new insights to overcome GC.

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Correspondence to: Dr Xiaoyan Yang, Institute of Pharmacy and Pharmacology, University of South China, 28 Western Changsheng Road, Hengyang, Hunan 421001, P.R. China
E-mail: yyangxiaoyan@163.com

1. Introduction

According to the newest data of WHO, cancer ranks second among global causes of death, cumulative amount of cancer deaths were 9.6 million, or one in six deaths, in 2018. The most ordinary cancers are lung, breast, colorectal, prostate, skin and stomach cancer (Table I; https://www.who.int/). The most ordinary deadly cancer are lung cancer, colorectal cancer, stomach cancer, liver cancer and breast cancer (Table II). From the above data, we can see that gastric cancer (GC) is in the top five positions in terms of mortality. GC has a severely bad impact on survival, constituting a significant issue.

The cause of GC is not fully understood. At present, relatively clear factors related to GC can be divided into exogenous and endogenous factors. Exogenous factors include lifestyle habits (e.g., low intake of fruits and vegetables, high intake of salts, nitrates, and pickled foods, alcoholism, smoking and obesity) (1-3), environmental factors, biological infections [e.g., *Helicobacter pylori (H. pylori)* (4) and Epstein-Barr virus infections (5,6), trauma and chronic irritation (e.g., chronic gastric ulcer)]. Hereditary factors (7,8) are endogenous (Table III).

MicroRNAs (miRNAs) are non-coding RNAs of ~22 nt nucleotides. The function of miRNAs is that they can avoid the translation of specific mRNAs and regulate several homeostatic and pathological processes within cells by acting as post-transcriptional regulators binding to the 3'-untranslated region (3'-UTR) of specific target mRNAs, specifically in the MRE (miRNA recognition element) sequence (9-11). Following deep exploration of miRNAs, it was identified that miRNAs can regulate gene expression in many normal and pathological cellular processes and become particularly attractive targets in the study of malignancies, including the study of GC. Several lines of study have verified that miRNA expression correlates with a variety of cancers, and abnormal expression occurs in many cancer types (12-14). Some miRNAs also have functions similar to tumor suppressor genes (such miRNAs are named tsmiRs) and oncogenes (such miRNAs are named oncomiRs) (15). The target gene of miRNA determines the role of specific miRNA. Some miRNAs could suppress tumor by targeting oncogenes and becoming tsmiRs. However, some miRNAs target tumor suppressor genes and become potential oncomiRs. The latest researches have verified that miRNAs are closely correlated with a series of oncogenesis

and development processes as well as the clinical application of GC (12-14). In summary, miRNAs are involved in the entire process of GC (Figs. 1 and 2).

2. Oncogenesis of gastric cancer and miRNAs

Cancer cells can uncontrollably grow and spread affect the body in an adverse manner. The most basic biological characteristics of tumor cells are imbalance in proliferation, abnormal differentiation, and ability to invade and metastasize. miRNAs are involved in oncogenesis of GC (Table IV).

OncomiRs. miR-761 plays a positive role in promoting the proliferation of human GC cells via negatively regulating glycogen synthase kinase 3β (GSK3β) (16). miR-21-5p directly targets pyruvate dehydrogenase A1 (PDHA1) (17) and SMAD7 (18) and suppresses PDHA1 and SMAD7, promoting glycolysis and cell proliferation of GC. miR-23, miR-27a and miR-24 promote GC cell proliferation via suppressing suppressor of cytokine induced signaling 6 (SOCS6) (19).

EBVaGC is an Epstein-Barr virus-associated GC, accounting for approximately 10% of all GC cases, and has distinctive pathological and molecular characteristics. Tumor protein p53 is encoded by the TP53 gene. p53 is one of the most important tumor suppressors and is activated by DNA damage and other stresses (20,21). EBV-miR-BART3-3p (BART3-3p) has a high expression state in EBVaGC and directly targets the CDS region of TP53 and inhibits PTEN to promote the proliferation and inhibit the senescence of GC cells (22). PTEN expression can affect cell apoptosis, proliferation, migration and intracellular mitochondria and inhibit AKT phosphorylation and suppress tumor growth (23,24). miR-205-5p may directly reduce PTEN expression and activity, then promote the growth of GC (25). miR-301b-3p attenuates zinc finger and BTB domain containing 4 (ZBTB4) expression and accelerates the growth of GC cells. The knockdown of miR-301b-3p markedly induces cell cycle arrest at G1 phase and apoptosis, finally inhibiting proliferation in MGC-803 cells (26). TIA-1 is a protein that inhibits proliferation and promotes apoptosis of GC cells. It was identified that TIA-1 presented a low level in GC tissues. miR-487a can promote the progression of GC by attenuating TIA-1 (27). RASSF1A can promote apoptosis via suppressing G1/S transition and cell proliferation in GC. miR-181a could promote gastric carcinogenesis, but RASSF1A knockdown could attenuate the effects of miR-181a downregulation. miR-181a promotes gastric carcinogenesis via downregulating RASSF1A. In addition, miR-181a can upregulate CDC25A, cyclin A2 and Bcl-2, and downregulate Bax protein expression in GC cell lines (28).

TsmiRs. *H. pylori* plays a very significant role in the oncogenesis and development of GC. CagA of *H. pylori* is an oncogenic factor in the processes of GC. NLRP3 can markedly initiate inflammation and is upregulated in GC. NLRP3 can promote the proliferation of epithelial cells and tumorigenesis of GC. A study identified that miR-22 is a suppressor of NLRP3. miR-22 can directly target NLRP3 and attenuate the oncogenic effects of it *in vitro* and *in vivo*. However, *H. pylori* infection would repress miR-22 expression but enhance NLRP3 expression, and that triggers extreme proliferation of epithelial cells and

the oncogenesis of GC. miR-22 can restrain *H. pylori*-induced gastric carcinogenesis via repressing NLRP3 (29). Stem cell-like cells, termed tumor stem cells, has the potential of self-renewal and differentiation which can produce high amounts of proliferating progeny cells through asymmetric division. The studies of Takaishi *et al* (30) and Ezeh *et al* (31) have confirmed the objective existence of GC stem cells. Relatively, miR-216a-3p could reduce the stemness of GC cells via suppressing Wnt/β-catenin signaling (32). It was verified that TSPAN8 is a target of miR-324-5p in GC and the expression of the two changes in opposite directions. miR-324-5p could downregulate TSPAN8 to reduce GC cell viability and induce apoptosis in SGC-7901 cells (33).

MAP3K10 is a target gene of miR-155-5p in GC cell lines. miR-155-5p mimics markedly reduce the expression level of MAP3K10 proteins in AGS-1 cells. miR-155-5p could downregulate MAP3K10 and then suppress GC cell proliferation and promote apoptosis (34). miR-1297 could reduce cell division control protein 6 (CDC6) expression to inhibit proliferation and promote apoptosis in GC cells (35). If there is miR-187 overexpression in MGC-803 cells, the cell proliferation will be suppressed and the cell cycle will be altered via capturing cells in the G0/G1 phase. MAD2 mitotic arrest deficient-like 2 (MAD2L2) and stomatin (EPB72)-like 2 (STOML2) are targets of miR-187. The expression of MAD2L2 and STOML2 is downregulated by overexpression of miR-187 in GC (36). Ying Yang 1 (YY1) is an important oncogene (37). YY1 was confirmed that it could destabilize p53 and HIF-1 to promote cell proliferation (38,39). Overexpression of miR-105 could reduce cell viability and proliferation in GC. YY1 is a direct target of miR-105, by downregulating which miR-105 has an anti-proliferative effect (40). HDAC9 knockout or miR-383-5p mimics both cause growth suppression and increase apoptosis in AGS and SGC-7901 cells. Furthermore, miR-383-5p could suppress HDAC9 to inhibit the cell proliferation of GC (41).

The protein kinase B (AKT1) signaling pathway promotes cell proliferation, growth and glucose metabolism, but inhibit apoptosis (42-44). The downregulation of miR-490-3p causes the enhancement of cell proliferation and suppression of apoptosis. In addition, overexpression of AKT1 partially reversed the effects of miR-490-3p in GC. It indicated that miR-490-3p reduced AKT1 to effect proliferation and apoptosis in GC cells (45). *In vitro*, miR-124-3p reduces cell viability and plate colony formation. *In vivo*, miR-124-3p suppresses tumor growth as well. miR-124-3p has a negative effect on tumor growth by negatively regulating SP1 and Rac1 in GC (46). The overexpression of miR-524-5p markedly reduces cell proliferation capacity and induces cell cycle arrest at G0/G1 phase in GC cells. Dual-luciferase, RT-qPCR and western blot analysis confirmed CASP3 as a target gene of miR-524-5p. Furthermore, recovery of CASP3 expression attenuated the negative effect of miR-524-5p on cell growth. In conclusion, miR-524-5p suppresses cell proliferation in GC via negatively adjusting CASP3 (47).

Using immune checkpoint blockades is a promising therapeutic strategy in the treatment of various human malignancies. miR-140 is significantly reduced in Hp-positive GC. PD-L1 is a direct target of miR-140 in GC. In addition, PD-L1 is significantly increased in Hp-positive GC. miR-140 significantly restrained GC cell proliferation through repressing PD-L1 (48). FZD7 is an important co-receptor in the WNT signaling

Table I. Most common cancers diagnosed per year worldwide.

Types of cancer	Number of patients
Lung cancer	2,090,000
Breast cancer	2,090,000
Colorectal cancer	1,800,000
Prostate cancer	1,280,000
Skin cancer (non-melanoma)	1,040,000
Stomach cancer	1,030,000

Table II. The most common lethal cancers worldwide.

Types of cancer	Death toll
Lung cancer	1,760,000
Colorectal cancer	862,000
Stomach cancer	783,000
Liver cancer	782,000
Breast cancer	627,000

Table III. Pathogenic factors of gastric cancer.

Pathogenic factors of gastric cancer	
Exogenous factors	Lifestyle habits
	Environmental factors
	Biological factors
	Trauma
	Chronic irritation
Endogenous factors	Hereditary factors

pathway and significantly induced by *H. pylori* infection in a dose- and time-dependent manner. miR-27b overexpression significantly inhibited *H. pylori* infection-induced cell proliferation and WNT signaling pathway activation in GC cells through negatively regulating Frizzled7 (49). Downregulation of SOCS2 can inhibit cell growth and cell-cycle progression in GC but SOCS2 is overexpressed in *H. pylori*-positive tissues. miR-101 restricts cell growth and tumorigenesis of *H. pylori*-related GC via repressing SOCS2 (50). FoxM1 is a critical positive regulator of cell proliferation and directly downregulated by miR-370 in GC. *H. pylori* and CagA restrain miR-370 expression, which promotes FoxM1 expression and cell proliferation (51). miR-99b is increased in *H. pylori*+ cancer samples and promotes *H. pylori*-induced autophagy to play a tumor-suppressive function through the inhibition of mTOR expression (52).

3. Oncogenesis and development of gastric cancer and miRNAs

Some miRNAs are correlated with the oncogenesis and development of GC (Table V).

OncomiRs. miR-718 could activate PI3K/Akt signaling, which directly downregulates PTEN and promotes the proliferation and invasion in GC (53). KLF2 binds to the PTEN promoter to induce its expression. miRNA-32-5p downregulates the expression of KLF2 to reduce PTEN and activate the PI3K/AKT signaling to enhance the development of GC (54). miR-21 markedly reduces PTEN level, which in turn increases Akt phosphorylation at Thr308 and Ser473. Conclusively, miR-21 enhances cell proliferation and migration via targeting PTEN/Akt signaling pathway in human GC cells (55). miR-15b-3p promotes the enhancement of migration, invasion, proliferation and inhibition of apoptosis by restraining DYNLT1, and cleaved caspase-9 expression in GC. In addition, caspase-9 induced Caspase-3 expression and then promoted apoptosis together (56).

miR-1290 increased the proliferation and invasiveness of GC cells via directly targeting and suppressing NKD1 (57). As a transcriptional regulator, NKD1 is a negative antagonist of the Wnt signaling pathway, which not only upregulates the expression of the downstream tumor suppressor gene, but also regulates the biological behavior of a variety of tumors in combination with the upstream related proteins (58-60). CagA of *H. pylori* can promote the expression of miR-584 and miR-1290 in an NF-κB and Erk1/2-dependent manner, respectively. miR-584 and miR-1290 can immediately inhibit Foxa1 to promote EMT. It indicates that miR-584 and miR-1290 induced by CagA can enhance EMT via repressing Foxa1 (61). miR-93-5p causes the occurrence of epithelial-mesenchymal transition and enhances proliferation by repressing AHNAK through Wnt signaling pathway in GC (62). miR-223-3p accelerates the cell cycle transition from the G1 to the S phase, which enhances DNA synthesis in the cell and cell proliferation. Arid1a is an essential constituent subunit of SWI/SNF, which is encoded by Arid1a (63). It plays a necessary role in the assembly of SWI/SNF complexes (64,65). Arid1a is a tumor depressor and target of miR-223-3p and miR-7641 in GC. Thus, miR-223-3p (66) and miR-7641 (67) enhance cell proliferation and invasion via downregulating Arid1a in GC. In addition, miR-647 could enhance proliferation, migration and invasion through repressing TP73 in GC (68). Furthermore, miR-223-3p/ARID1A axis is involved in CagA-induced cell proliferation and migration. miR-223-3p is significantly higher in *H. pylori*-positive GC tissues than that in *H. pylori*-negative tissues. NF-κB/miR-223-3p/ARID1A axis may link the process of *H. pylori*-induced chronic inflammation to GC (69).

SFRP1 and MEG3 are targets of miR-208a, which enhances cell proliferation and invasion by passively regulating MEG3 and SFRP1 in GC (70). miR-183-5p.1 plays a positive role in the promotion of cell proliferation, migration and invasion through repressing TPM1 and the Bcl-2/P53 signaling pathways in GC (71). c-MYB may regulate proliferation, growth, differentiation and survival of many cell types (72). The expression changes of miR-155 and c-MYB are opposite in GC. In addition, c-MYB was a direct target of miR-155. miR-155 was able to inhibit c-MYB, which promotes the metastasis, growth and tube formation of vascular cells and leads to the occurrence and development of tumors (73). FOXO3a inhibited angiogenesis via suppressing the growth of vascular smooth muscle (74). miR-155 is an angiogenesis driver. It can accelerate the generation of new vessels through

Figure 1. The regulatory mechanisms of oncomiRs in gastric cancer.

Figure 2. The regulatory mechanisms of tsmiRs in gastric cancer.

inhibiting Forkhead box O3 (FOXO3a) protein (75). Similar to miR-155, miR-130a also activates angiogenesis of GC cells through repressing c-MYB in vascular endothelial cells (76). *H. pylori* increased the expression of miR-543 in GC and increased miR-543 induced by CagA is a strong promoter of cell proliferation, migration, and invasion via SIRT1. miR-543 significantly restrained SIRT1 in GC (77).

miR-222-3p aberrantly upregulates in GC. miR-222-3p is significantly upregulated in the *H. pylori* (+) group and homeodomain-interacting protein kinase 2 (HIPK2) is a novel target of miR-222-3p in GC. HIPK2 levels were decreased in *H. pylori* (+) GC patients. miR-222-3p overexpression promoted the proliferation and invasion via repressing HIPK2 in GC infected by *H. pylori* (78).

Table IV. The roles of miRNAs in oncogenesis of gastric cancer.

	miRNAs	Targets/signaling	The relationship between miRNA and targets/pathway	(Refs.)
OncomiRs	miR-761	GSK3β	Negative	(16)
	miR-21-5p	PDHA1,	Negative	(17)
		SMAD7	Negative	(18)
	miR-23, miR-27a, miR-24	SOCS6	Negative	(19)
	EBV-miR-BART3-3p	TP53	Negative	(22)
		PTEN		
	miR-205-5p	PTEN	Negative	(25)
	miR-301b-3p	ZBTB4	Negative	(26)
	miR-487a	TIA-1	Negative	(27)
	miR-181a	RASSF1A	Negative	(28)
	miR-22	NLRP3	Negative	(29)
	miR-216a-3p	Wnt/β-catein signaling	Negative	(32)
	miR-324-5p	TSPAN8	Negative	(33)
	miR-155-5p	MAP3K10	Negative	(34)
	miR-1297	CDC6	Negative	(35)
	miR-187	MAD2L2	Negative	(36)
		STDML2		
TsmiRs	miR-105	YY1	Negative	(40)
	miR-383-5p	HDAC9	Negative	(41)
	miR-490-3p	AKT1	Negative	(45)
	miR-124-3p	SP1	Negative	(46)
		Rac1		
	miR-524-5p	CASP3	Negative	(47)
	miR-140	PD-L1	Negative	(48)
	miR-27b	FZD7	Negative	(49)
	miR-101	SOCS2	Negative	(50)
	miR-370	FoxM1	Negative	(51)
	miR-99b	mTOR	Negative	(52)

TsmiRs. miR-133b may become a tumor suppressor because of repressing the proliferation and invasion of GC cells through affecting ATP citrate lyase (ACLY) and peroxisome prolifer-ator-activated receptor-γ (PPARγ) in GC, which inhibits ACLY and increases the levels of nuclear PPARγ (79). IGFBP1 is a target of miR-519a and they have an inverse relationship in GC cells. Therefore, miR-519a could suppress the proliferation, migration and invasion of GC cells via attenuating IGFBP1 (80). Similarly, S100A16 is a target of miR-6884-5p and they have an opposite relationship in GC tissues and cell lines. miR-6884-5p inhibited the proliferation, invasion and EMT via attenuating S100A16 expression (81). Presenilin 1 (PSEN1) was a direct target of miR-133a, the suppression of which would abolish the promoting functions of miR-133a suppression on cell growth and metastasis. miR-133a represses GC cell growth, migration, and epithelial-mesenchymal transition by attenuating prese-nilin 1 (82). In addition, miR-6852 could attenuate forkhead box J1 (FOXJ1) to suppress cell proliferation and invasion in GC (83). Upregulation of miR-153 in the GC SNU-5 cells repress cell proliferation, migration and invasion. The expres-sion of Kruppel-like factor 5 (KLF5) is negatively regulated by miR-153 in SNU-5 cells (84).

miR-200a-3p overexpression increases the G1/S cell ratio and attenuates cell proliferation and colony formation and directly interacts with the 3'-UTR of KLF12. However, there is a negative correlation between miR-200a-3p and KLF12. These indicated that miR-200a-3p repressed cell proliferation via downregulating KLF12 (85). miR-520a-3p could markedly inhibit the cell proliferation, invasion and migration of SGC-7901 and MGC-803 cell lines. Spindle and kinetochore-associated 2 (SKA2) is a target gene of miR-520a-3p. miR-520a-3p plays a tumor suppressor effect via down-regulating SKA2 in GC cell lines (86). miR-454 could target zinc finger E-box-binding homeobox 1 (ZEB1) and repress its expression. Therefore, miR-454 attenuates the proliferation, migration and invasion by repressing ZEB1 in GC (87). EPS8 is downregulated by miR-345 and Rac1 signaling is its downstream. miR-345 could attenuate migration and the stem-like cell phenotype via inactivation of Rac1 by down-regulating EPS8 in GC (88). Overexpression of miR-495 suppressed cell proliferation and migration of GC, which could promote caspase-3/-9 and Bax protein expression and suppress cyclin D1 protein expression and the PI3K/Akt/mTOR pathway (89). In addition, overex-pression of miR-375 attenuated the AKT/mammalian target

Table V. The roles of miRNAs in both oncogenesis and development of gastric cancer.

	miRNAs	Target/signaling	The relationship between miRNA and target/pathway	(Refs.)
OncomiRs	miR-718	PI3K/Akt signaling	Positive	(53)
		PTEN	Negative	
	miR-32-5p	KLF2	Negative	(54)
		PTEN		
		PI3K/Akt signaling	Positive	
	miR-21	PTEN,	Negative	(55)
		PI3K/Akt signaling	Positive	
	miR-15b-3p	DYNLT1	Negative	(56)
		Caspase-9		
		Caspase-3		
	miR-1290	NKD1	Negative	(57,61)
		Foxa1		
	miR-584	Foxa1	Negative	(61)
	miR-93-5p	AHNAK	Negative	(62
	miR-223-3p			
	miR-7641	ARID1A	Negative	(66,67)
	miR-647	TP73	Negative	(68)
	miR-208a	MEG3	Negative	(70)
		SFRP1		
	miR-183-5p.1	TPM1	Negative	(71)
		Bcl-2/P53		
	miR-155	C-MYB	Negative	(73)
		VEGF		
		FOXO3a	Negative	(75)
	miR-130a	c-MYB	Negative	(76)
	miR-543	SIRT1	Negative	(77)
	miR-222-3p	HIPK2	Negative	(78)
	miR-133b	ACLY	Negative	(79)
		PPARγ	Positive	
	miR-519a	IGFBP1	Negative	(80)
TsmiRs	miR-6884-5p	S100A16	Negative	(81)
	miR-133a	PSEN1	Negative	(82)
	miR-6852	FOXJ1	Negative	(83)
	miR-153	KLF5	Negative	(84)
	miR-200a-3p	KLF12	Negative	(85)
	miR-520a-3p	SKA2	Negative	(86)
	miR-454	ZEB1	Negative	(87)
	miR-345	EPS8	Negative	(88)
		Rac1 signaling		
	miR-495	Caspase-3	Positive	(89)
		Caspase-9		
		Bax		
		PI3K/Akt/mTOR	Negative	
		Cyclin D1		
	miR-375	Akt/mTOR signaling	Negative	(90)
		AK2-STAT3 signaling	Negative	(91)
	miR-1915	RAGE	Negative	(92)

of rapamycin signaling pathway to suppress the proliferation and migration of GC cells (90). In addition, miR-375 repressed *H. pylori*-induced gastric carcinogenesis by attenuating JAK2-STAT3 signaling (91). miR-1915 was under-expressed but RAGE was overexpressed in *H. pylori*-infected GC tissues and cells. Overexpression of miR-1915 restrains the

Table VI. The roles of miRNAs in development of gastric cancer.

	miRNAs	Target/signaling	The relationship between miRNA and target/pathway	(Refs.)
OncomiRs	miR-574-5p	PTPN3	Negative	(93)
	miR-21-5p	SMAD7	Negative	(94)
		TGF-β/SMAD signaling	Positive	(94)
	miR-196a-1	SFRP1	Negative	(95)
	miR-192/215	RAB11-FIP2	Negative	(96)
	miR-29a-3p	A20	Negative	(97)
	miR-761	Ras	Negative	(98)
		RIN1		
	miR-28-5p	AKT	Negative	(99)
	miR-337-3p	ARHGAP10	Negative	(101)
	miR-449c	PFKFB3	Negative	(104)
	miR-711	CD44	Negative	(105)
TsmiRs		vimentin		
		E-cadherin	Positive	
	miR-203	Annexin A4	Negative	(106)
		CASK	Negative	(107)
	miR-217	PTPN14	Negative	(108)
	miR-381	SOX4	Negative	(109)
	miR-143-3p	AKT2	Negative	(110)
	miR-30a	COX-2	Negative	(111)
		BCL9		

proliferation, invasion, and migration of *H. pylori*-infected GC by repressing RAGE (92).

4. Development of gastric cancer and miRNAs

Some miRNAs are correlated with the development of GC (Table VI).

OncomiRs. miR-574-5p bound to the 3'-UTR of protein tyrosine phosphatase non-receptor type 3 (PTPN3) mRNA, which represses PTPN3 to enhance phosphorylation of p44/42 MAPKs and promote angiogenesis in GC (93). Peritoneal mesothelial cells (PMCs) promoted peritoneal metastasis of GC cells via mesothelial-to-mesenchymal transition (MMT), which provides a convenient environment for metastatic GC cells. miR-21-5p could repress SMAD7 expression and induce MMT of PMCs and promote tumor peritoneal metastasis through activation of TGF-β/SMAD pathway (94). SFRP1 is one of the antagonists of the Wnt/β-catenin signaling pathway, the 3-UTR of which could bind miR-196a-1. Therefore, miR-196a-1 plays a positive effect in promoting GC cell invasion and metastasis by repressing SFRP1 (95). RAB11-FIP2 is a target of miR-192/215 that affects the establishment of cell polarity and tight junction formation in GC cells via attenuating RAB11-FIP2 (96). Similarly, *H. pylori* infection can upregulate the expression of miR-29a-3p in GC, while A20 expression is decreased in *H. pylori*-positive gastric mucosa tissues. miR-29a-3p can enhance the migration of gastric epithelial cells. A20 is a direct target of miR-29a-3p and the miR-29a-3p mimic significantly blocked A20 expression. The

miR-29a-3p is a tumor promotive miRNA and enhances migration through directly repressing A20 gene in *H. pylori*-infected GC (97).

TsmiRs. miR-761 suppressed the expression of Ras and Rab interactor 1 (RIN1) to play a repressive role in the metastasis of GC (98). miR-28-5p, a tumor suppressor, represses the phosphorylation of RAC serine/threonine protein kinase (AKT) that affects invasion and metastasis to inhibit GC cell migration and invasion (99). ARHGAP10 has a passive effect in regulating the small G protein Rho- and Cdc42-mediated downstream signal transduction (100). miR-337-3p bound to the 3'-untranslated region of ARHGAP10 and repressed the mRNA and protein levels of ARHGAP10 to attenuate gastric tumor metastasis (101). It has been reported that PFKFB3 was a versatile protein in human cancers (102,103). It is a cancer-promoting protein and a target of miR-449c. Overexpression of PFKFB3 abrogates the inhibitory effect of miR-449c on the migration and invasion of GC cells (104).

miR-711 could repress vimentin protein expression but upregulate E-cadherin protein expression, which causes the downregulation of CD44 to inhibit EMT of GC cells (105). In GC tissues and cell lines, the expression changes between miR-203 and Annexin A4 are opposite and the invasion and EMT are suppressed by overexpression of miR-203 via repressing Annexin A4 (106). In addition miR-203 is also a tumor suppressor in *H. pylori*-related GC via repressing CASK expression (107). PTPN14 is a target of miR-217. miR-217 abrogated PTPN14 expression by directly targeting its 3'-UTR

and epithelial-to-mesenchymal transition, metastasis and invasion through repressing PTPN14 in GC (108). SRY-Box 4 (SOX4) plays a stimulatory effect on epithelial-mesenchymal transition in GC. miR-381 could abrogate migration and invasion in human gastric carcinoma via downregulating it (109). A study identified that miR-143-3p was significantly increased in *H. pylori*-positive GC tissues but decreased in GC tissues and cells. AKT2 is a certain direct target of miR-143-3p and they have an opposite relationship. Knockdown of miR-143-3p can promote AKT2 expression. miR-143-3p acts as a novel tumor suppressive miRNA via repressing migration and invasion by directly targeting AKT2 gene (110). A study identified that miR-30a acts as a tumor suppressor to inhibit migration of *H. pylori*-infected GC by double-restraining COX-2 and BCL9 (111).

5. Diagnosis of gastric cancer and miRNAs

Some miRNAs could become potential diagnostic candidates during the early stage of GC (Table VII).

OncomiRs. miR-21 and miR-222 present high expression state in GC plasma (112). The signet-ring cell carcinoma (SRC) is one of the histological subtypes of GC, which has strong intrusion capability and always occurs in terminal patients. who present high miR-99a-5p expression of SRC (113). Compared with normal tissues and cells, the levels of miR-17 and miR-25 are significantly high in the GC tissues and cells. The phenomenon can be seen at an early stage and is helpful for the detection of GC (114). In GC patients, the level of miR-214 and tumor size, lymphatic metastasis, TNM stage, CEA expression and CA19-9 expression were positively correlated. miR-214 is an independent factor affecting patient diagnosis (115). Overexpression of exosomal miR-1246 in serum often occurs in GC patients. ROC analysis verified that circulating exosomal miR-1246 expression could be a good index for distinguishing GC patients from healthy controls (12).

TsmiRs. Kaplan-Meier survival analysis is a common method used to determine whether a certain miRNA can become a diagnostic marker. miR-181b-5p is significantly decreased in GC-associated malignant ascites (116). Compared with normal tissues, miR-551b-5p emerged a low expression state in GC tissues. Furthermore, it is verified that the downregulation of miR-551b-5p indicates the appearance of GC by serum miRNA microarray analysis (117). As with the miRNAs mentioned above, miR-133b (114) and miRNA-381 (118) were markedly decreased in GC patient groups compared with normal cases. In addition, these miRNAs are associated with lymph node metastasis and the development of GC. Thus, miR-133b and miR-381 are potential candidates for the diagnosis in GC patients in the early stage.

6. Treatment of gastric cancer and miRNAs

Some miRNAs can be used to treatment GC patients (Table VIII).

OncomiRs. miR-501 directly regulates BLID at the post-transcriptional level in multiple GC cell lines. Furthermore,

Table VII. The roles of miRNAs in diagnosis of gastric cancer.

	miRNAs	Expression in gastric cancer	(Refs.)
OncomiRs	miR-21, miR-222	Upregulate	(112)
	miR-99a-5p	Upregulate	(113)
	miR-17, miR-25	Upregulate	(114)
	miR-214	Upregulate	(115)
	miR-1246	Upregulate	(12)
	miR-181b-5p	Downregulate	(116)
TsmiRs	miR-551b-5p	Downregulate	(117)
	miR-133b	Downregulate	(114)
	miR-381	Downregulate	(118)

in doxorubicin-resistant GC SGC7901/ADR cells, endogenous miR-501 was higher but BLID was lower than parental SGC7901 cells. miR-501 could therefore become a tumor suppressor because it inhibited GC cell apoptosis and enhanced cell proliferation, migration, and invasion to induce resistance to doxorubicin. The suppression of BLID by miR-501 subsequently inactivates caspase-9 and caspase-3 and phosphorylation of Akt (119). In a similar manner to miR-501 and BLID, miR-17 presents high expression but DEDD presents low expression in GC. DEDD is a target gene of miR-17. In a study, it has been verified that miR-17 could induce resistance to cisplatin or 5-Fu and suppress cell apoptosis via repressing DEDD in GC cells (120). Cell death occurs in various ways, including ferroptosis which is induced by lipid-ROS in an iron-dependent manner. However, miR-522 inhibited ferroptosis by targeting ALOX15 and repressing lipid-ROS accumulation in cancer cells. Cancer-associated fibroblasts (CAFs) secretes various bioactive substances to promote tumor progression and drug resistance including exosomes. In addition, CAFs secrete miR-522 in the tumor microenvironment and consequently promote acquired chemo-resistance by suppressing ferroptosis in GC (121). miR-21 is a typical oncomiRNA, the overexpression of which is ordinary in GC cells. Phosphatase and tensin homolog (PTEN) is a typical tumor suppressor that passively regulates the Akt/PKB signaling pathway by repressing phosphoinositide 3-kinase (PI3K), a target of miR-21 in cancer cells (122,123). miR-21 enhances the chemo-resistance of DDP and curcumin, as well as tumor growth, migration and invasion via abrogating autophagy through the miR-21/PTEN/PI3K/Akt/mTOR pathway in GC cells (124,125). Overexpression of miR-4295 is relevant to the higher expression of EGFR, PI3K, Akt, p-PI3K and p-Akt and the lower expression of LRIG1 in GC cells. In addition, miR-4295 directly targets LRIG1. In a recent study, it was confirmed that miR-4295 could activate the EGFR/PI3K/Akt signaling pathway via negatively regulating LRIG1 expression, which then promoted cell proliferation and abrogated apoptosis-induced DDP in GC cells (126).

miR-96 repressed the post-transcriptional expression of FOXO1. Subsequently, the downexpression of FOXO1 led to downregulation of transcriptional activity of the cyclin-dependent kinase inhibitor 1A (CDKN1A, also known

Table VIII. The roles of miRNAs in treatment of gastric cancer.

	miRNAs	Target/Signaling	The relationship between miRNA and target/pathway	(Refs.)
OncomiRs	miR-501-5P	BLID	Negative	(119)
	miR-17	DEDD	Negative	(120)
	miR-522	ALOX15	Negative	121)
	miR-21	PTEN	Negative	(122,123)
		PI3K/Akt/mTOR signaling	Positive	(124,125)
	miR-4295	LRIG1	Negative	(126)
		EGFR/PI3K/Akt signaling	Positive	(126)
	miR-96	FOXO1	Negative	(127)
	miR-106a-3p	JAK2/STAT3 signaling	Positive	(128)
		SOCS		
	miR-135b-5p	KLF4	Negative	(129)
	miR-20a	MICA	Negative	(131)
	miR-141	KEAP1	Negative	(132)
	miR-155-5p	GATA3	Negative	(133)
		TP53INP1		
TsmiRs	miR-362-5p	SUZ12	Negative	(134)
	miR-200c	ERCC3	Negative	(135)
		ERCC4		
	miR-145	MEK/ERK signaling	Negative	(136)
		NF-κB signaling		
	miR-876-3p	TMED3	Negative	(137)
	miR-320a	β-catenin ABCG2	Negative	(138)
	miR-4496			

Table IX. The roles of miRNAs in prognosis of gastric cancer.

	miRNAs	(Refs.)
OncomiRs	miR-501-5p	(119)
	miR-208a	(70)
	miR-718	(53)
	miR-15b-3p	(56)
	miR-519a	(80)
	miR-153	(84)
	miR-187	(36)
TsmiRs	miR-345	(88)
	miR-28-5p	(99)
	miR-124-3p	(46)
	miR-383-5p	(41)

as p21) promoter region. Consequently, the expression of p21 would be downregulated in a tumor protein p53-independent manner. It was recently identified that the induction of miR-96 could cause chemoresistance and promote proliferation via repressing FOXO1 and p21 in SGC7901 cells (127). Apatinib is a common chemotherapy drug used in the treatment of GC. miR-106a-3p actived Janus-Activated Kinase 2 (JAK2)/Signal Transducer and Activator of Transcription 3 (STAT3) by increasing the level of SOCS family, which induced resistance of Apatinib (128). *H. pylori* infection could induce the secretion of many substances in GC, including miR-135b-5p. miR-135b-5p abrogates KLF4 expression by directly targeting its 3'-UTR to induce cisplatin resistance in *H. pylori* GC cells (129). NK cells could directly kill tumor cells, and NKG2D plays an essential role in mediating the anti-tumor immunity of NK cells. NKG2D specifically binds to its ligand MICA (MHC class I chain-related protein A), transmits an activation signal through an adaptor protein (DAP10 or DAP12), and mobilizes particles containing perforin and granzyme B to connect with tumor cells to cause the tumor cells to lyse to exert antitumor effects. MICA suppressed the immune-evasion of GC cells. However, miR-20a could repress MICA expression by directly targeting MICA (130). Upregulation of miR-20a could promote the harmful effect of Docetaxel on abrogation of MICA to repress the curative effect of Docetaxel (131). To some extent, *H. pylori* infection is good for the treatment of GC. *H. pylori* infection significantly downregulates miR-141. Knockdown of miR-141 expression significantly improves cisplatin sensitivity via suppressing KEAP1. KEAP1 is a direct target of miR-141 (132).

TsmiRs. miR-155-5p has a large number of targets, which includes GATA binding protein 3 (GATA3) and tumor protein p53 inducible nuclear protein 1 (TP53INP1). miR-155-5p could interact with their 3'-untranslated regions. Exosome miR-155-5p

can induce EMT and the transition of chemo-resistant phenotypes from paclitaxel-resistant GC cells to the sensitive cells, the mechanism of which may is that miR-155-5p suppresses the expression of GATA3 and TP53INP1 (133). Suppressor of zeste 12 protein (SUZ12) is one of the targets of miR-362-5p. It is relevant to the stimulatory effect of miR-362-5p on cisplatin sensitivity of GC cells. In a recent study, it was verified that miR-362-5p could promote cisplatin sensitivity via repressing SUZ12 (134). Numerous miRNAs are relevant to reversal of drug resistance in human GC cells. miR-200c is a miRNAs whose overexpression may reverse drug resistance in the SGC7901/DDP GC cell line via repressing ERCC3 and ERCC4 through the NER-ERCC3/4 pathway (135). Lidocaine is an anti-cancer chemotherapy drug which abrogates the viability, proliferation, migration, and invasion of GC cells. miR-145 plays a positive role in promoting the effect of lidocaine on GC cells. It was confirmed that lidocaine could have a stronger inhibitory action via up-regulating miR-145 expression which further inactivates the MEK/ERK and NF-κB signaling pathways (136). TMED3 is one of the direct targets of miR-876-3p. miR-876-3p inhibitor may significantly increase mRNA and protein expression of TMED3, which represses cisplatin sensitivity and restricts stem cell-like features of GC (137). miR-320a and miR-4496 attenuate *H. pylori* cytotoxin-associated gene A (CagA)-induced chemoresistance by repressing β-catenin and ATP-binding cassette, subfamily G, member 2 (ABCG2) (138).

7. Prognosis of gastric cancer and miRNAs

Some miRNAs could serve as potential prognosis targets for GC patients (Table IX).

OncomiRs. Some miRNAs are abnormally expressed in patients after treatment and these abnormal expressions can become indicators of poor prognosis. miR-501 presents a high expression state in patients with poor prognosis, thereby making it an indicator thereof (119). Kaplan-Meier analysis is also used to discern indicators of poor prognosis. Kaplan-Meier analysis confirmed that overexpression of miR-208a was obviously associated with shorter overall survival (OS) time. Furthermore, univariate and multivariate Cox analysis revealed that lymph node metastasis, TNM stage and higher miR-208a were independent risks factors of OS time (70). In conclusion, miR-208a is another indicator of poor prognosis of GC. Similarly, miR-718 (53) and exo-miR-15b-3p (56) are upregulated in patients with poor prognosis and indicators of worse overall survival and poor prognosis.

TsmiRs. There is no doubt that there are some miRNAs abnormally expressed in patients after treatment and these abnormal expressions can become indicators of good prognosis as well. Increased expression of miR-519a is relevant to the good overall survival of GC patients and is identified as an independent prognostic biomarker for the patients (80). miR-153 (84) and miR-187 (36) are reduced in GC patients with aggressiveness and poor prognosis. Furthermore, downregulation of the two miRNAs is correlated to cell differentiation, TNM staging and poor prognosis in GC patients. These miRNAs could also be indicators of good

prognosis in GC patients after treatment. As with miR-153 and miR-187, GC patients with a stronger expression of miR-345 have a better prognosis (88). Compared with GC patients with lower miR-28-5p expression, patients with higher expression have a longer overall survival time and good prognosis, as indicated via the Kaplan Meier survival curve analysis (99). Kaplan-Meier analysis also revealed that the downregulation of miR-124-3p (46) and miR-383-5p (41) correlates with advanced clinical stage, larger tumor size, lymph node metastases and shorter OS time. Furthermore, multivariate Cox proportional hazards regression analyses revealed that miR-124-3p and miR-383-5p were independent prognostic factors for predicting the prognosis of GC patients after treatment.

8. Conclusion and future perspectives

The relationship between miRNAs and GC is very close, miRNAs can be divided into oncomiRNA and tsmiRNA. miRNAs correlate with the entire clinical course of GC, but currently there are not many miRNAs that can be truly used in clinical practice. Since the specific mechanism of most miRNAs is not yet clear, the current review uses the clinical process of GC as a clue to comprehensively elaborate the latest miRNAs with specific targets or pathways and GC research results, which are of great significance for the prevention, diagnosis, treatment and prognosis of GC. As miRNAs are relevant to various tumors, this review can also provide ideas for other tumor research.

Authors' contributions

JO and XY contributed to writing the original draft. ZX, XL, GT and RG contributed to revising the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors have no competing interests to disclose.

References

1. Lunet N, Valbuena C, Vieira AL, Lopes C, Lopes C, David L, Carneiro F and Barros H: Fruit and vegetable consumption and gastric cancer by location and histological type: Case-control and meta-analysis. Eur J Cancer Prev 16: 312-327, 2007.
2. Ladeiras-Lopes R, Pereira AK, Nogueira A, Pinheiro-Torres T, Pinto I, Santos-Pereira R and Lunet N: Smoking and gastric cancer: Systematic review and meta-analysis of cohort studies. Cancer Causes Control 19: 689-701, 2008.
3. Yang P, Zhou Y, Chen B, Wan HW, Jia GQ, Bai HL and Wu XT: Overweight, obesity and gastric cancer risk: Results from a meta-analysis of cohort studies. Eur J Cancer 45: 2867-2873, 2009.
4. Bornschein J, Selgrad M, Warnecke M, Kuester D, Wex T and Malfertheiner P: H. pylori infection is a key risk factor for proximal gastric cancer. Dig Dis Sci 55: 3124-3131, 2010.
5. Wu MS, Shun CT, Wu CC, Hsu TY, Lin MT, Chang MC, Wang HP and Lin JT: Epstein-Barr virus-associated gastric carcinomas: Relation to H. pylori infection and genetic alterations. Gastroenterology 118: 1031-1038, 2000.
6. Wang HH, Wu MS, Shun CT, Wang HP, Lin CC and Lin JT: Lymphoepithelioma-like carcinoma of the stomach: A subset of gastric carcinoma with distinct clinicopathological features and high prevalence of Epstein-Barr virus infection. Hepatogastroenterology 46: 1214-1219, 1999.
7. Oliveira C, Pinheiro H, Figueiredo J, Seruca R and Carneiro F: Familial gastric cancer genetic susceptibility, pathology, and implications for management. Lancet Oncol 16: e60-e70, 2015.
8. Van Cutsem E, Sagaert X, Topal B, Haustermans K and Prenen H: Gastric cancer. Lancet 388: 2654-2664, 2016.
9. Farazi TA, Hoell JI, Morozov P and Tuschl T: MicroRNAs in human cancer. dv Exp Med Biol 774: 1-20, 2013.
10. He L and Hannon GJ: MicroRNAs: Small RNAs with a big role in gene regulation. Nat Rev Genet 5: 522-531, 2004.
11. Bartel DP: MicroRNAs: Target recognition and regulatory functions. Cell 136: 215-233, 2009.
12. Shi Y, Wang Z, Zhu X, Chen L, Ma Y, Wang J, Yang X and Liu Z: Exosomal miR-1246 in serum as a potential biomarker for early diagnosis of gastric cancer. Int J Clin Oncol 25: 89-99, 2020.
13. Ishikawa D, Yoshikawa K, Takasu C, Kashihara H, Nishi M, Tokunaga T, Higashijima J and Shimada M: Expression level of MicroRNA-449a predicts the prognosis of patients with gastric cancer. Anticancer Res 40: 239-244, 2020.
14. Chen P, Guo H, Wu X, Li J, Duan X, Ba Q and Wang H: Epigenetic silencing of microRNA-204 by Helicobacter pylori augments the NF-κB signaling pathway in gastric cancer development and progression. Carcinogenesis 41: 430-441, 2020.
15. Garzon R, Marcucci G and Croce CM: Targeting microRNAs in cancer: Rationale, strategies and challenges. Nat Rev Drug Discov 9: 775-789, 2010.
16. Sun X, Hou H, Li K and Zheng M: microRNA-761 regulates glycogen synthase kinase 3β expression and promotes the proliferation and cell cycle of human gastric cancer cells. Oncol Lett 16: 3459-3464, 2018.
17. Liu Z, Yu M, Fei B, Fang X, Ma T and Wang D: miR-21-5p targets PDHA1 to regulate glycolysis and cancer progression in gastric cancer. Oncol Rep 40: 2955-2963, 2018.
18. Jiang Y, Zhang M, Guo T, Yang C, Zhang C and Hao J: MicroRNA-21-5p promotes proliferation of gastric cancer cells through targeting SMAD7. Onco Targets Ther 11: 4901-4911, 2018.
19. Hua K, Chen YT, Chen CF, Tang YS, Huang TT, Lin YC, Yeh TS, Huang KH, Lee HC, Hsu MT, et al: MicroRNA-23a/27a/24-2 cluster promotes gastric cancer cell proliferation synergistically. Oncol Lett 16: 2319-2325, 2018.
20. Sherr CJ: Principles of tumor suppression. Cell 116: 235-246, 2004.
21. Vogelstein B, Lane D and Levine AJ: Surfing the p53 network. Nature 408: 307-310, 2000.
22. Wang J, Zheng X, Qin Z, Wei L, Lu Y, Peng Q, Gao Y, Zhang X, Zhang X, Li Z, et al: Epstein-Barr virus miR-BART3-3p promotes tumorigenesis by regulating the senescence pathway in gastric cancer. J Biol Chem 294: 4854-4866, 2019.
23. Xu LF, Wu ZP, Chen Y, Zhu QS, Hamidi S and Navab R: MicroRNA-21 (miR-21) regulates cellular proliferation, invasion, migration, and apoptosis by targeting PTEN, RECK and Bcl-2 in lung squamous carcinoma, Gejiu City, China. PLoS One 9: e103698, 2014.
24. Chen X, Wang W, Zhang J, Li S, Zhao Y, Tan L and Luo A: Involvement of caspase-3/PTEN signaling pathway in isoflurane-induced decrease of self-renewal capacity of hippocampal neural precursor cells. Brain Res 1625: 275-286, 2015.
25. Yao L, Shi W and Gu J: Micro-RNA 205-5p is involved in the progression of gastric cancer and targets phosphatase and tensin homolog (PTEN) in SGC-7901 human gastric cancer cells. Med Sci Monit 25: 6367-6377, 2019.
26. Fan H, Jin X, Liao C, Qiao L and Zhao W: MicroRNA-301b-3p accelerates the growth of gastric cancer cells by targeting zinc finger and BTB domain containing 4. Pathol Res Pract 215: 152667, 2019.
27. Yang X, Wang M, Lin B, Yao D, Li J, Tang X, Li S, Liu Y, Xie R and Yu S: miR-487a promotes progression of gastric cancer by targeting TIA1. Biochimie 154: 119-126, 2018.
28. Yu J, Qi J, Sun X, Wang W, Wei G, Wu Y, Gao Q and Zheng J: MicroRNA-181a promotes cell proliferation and inhibits apoptosis in gastric cancer by targeting RASSF1A. Oncol Rep 40: 1959-1970, 2018.
29. Li S, Liang X, Ma L, Shen L, Li T, Zheng L, Sun A, Shang W, Chen C, Zhao W and Jia J: miR-22 sustains NLRP3 expression and attenuates H. pylori-induced gastric carcinogenesis. Oncogene 37: 884-896, 2018.
30. Takaishi S, Okumura T and Wang TC: Gastric cancer stem cells. J Clin Oncol 26: 2876-2882, 2008.
31. Ezeh UI, Turek PJ, Reijo RA and Clark AT: Human embryonic stem cell genes OCT4, NANOG, STELLAR, and GDF3 are expressed in both seminoma and breast carcinoma. Cancer 104: 2255-2265, 2005.
32. Song H, Shi L, Xu Y, Xu T, Fan R, Cao M, Xu W and Song J: BRD4 promotes the stemness of gastric cancer cells via attenuating miR-216a-3p-mediated inhibition of Wnt/β-catenin signaling. Eur J Pharmacol 852: 189-197, 2019.
33. Lin H, Zhou AJ, Zhang JY, Liu SF and Gu JX: miR-324-5p reduces viability and induces apoptosis in gastric cancer cells through modulating TSPAN8. J Pharm Pharmacol 70: 1513-1520, 2018.
34. Li S, Zhang T, Zhou X, Du Z, Chen F, Luo J and Liu Q: The tumor suppressor role of miR-155-5p in gastric cancer. Oncol Lett 16: 2709-2714, 2018.
35. Zhang X, Zhang M, Guo Q, Hu X, Zhao Z, Ni L, Liu L, Wang X, Wang Z, Tong D, et al: MicroRNA-1297 inhibits proliferation and promotes apoptosis in gastric cancer cells by downregulating CDC6 expression. Anticancer Drugs 30: 803-811, 2019.
36. Chen W, Cui Y, Wang J, Yuan Y, Sun X, Zhang L, Shen S and Cheng J: Effects of downregulated expression of microRNA-187 in gastric cancer. Exp Ther Med 16: 1061-1070, 2018.
37. Shi Y, Lee JS and Galvin KM: Everything you have ever wanted to know about Yin Yang 1. Biochim Biophys Acta 1332: F49-F66, 1997.
38. Sui G, Affar el B, Shi Y, Brignone C, Wall NR, Yin P, Donohoe M, Luke MP, Calvo D, Grossman SR and Shi Y: Yin Yang 1 is a negative regulator of p53. Cell 117: 859-872, 2004.
39. Wu S, Kasim V, Kano MR, Tanaka S, Ohba S, Miura Y, Miyata K, Liu X, Matsuhashi A, Chung UI, et al: Transcription factor YY1 contributes to tumor growth by stabilizing hypoxia factor HIF-1α in a p53-independent manner. Cancer Res 73: 1787-1799, 2013.
40. Zhou GQ, Han F, Shi ZL, Yu L, Li XF, Yu C, Shen CL, Wan DW, Zhu XG, Li R and He SB: DNMT3A-mediated down-regulation of microRNA-105 promotes gastric cancer cell proliferation. Eur Rev Med Pharmacol Sci 21: 3377-3383, 2017.
41. Xu G, Li N, Zhang Y, Zhang J, Xu R and Wu Y: MicroRNA-383-5p inhibits the progression of gastric carcinoma via targeting HDAC9 expression. Braz J Med Biol Res 52: e8341, 2019.

42. Ooms LM, Binge LC, Davies EM, Rahman P, Conway JR, Gurung R, Ferguson DT, Papa A, Fedele CG, Vieusseux JL, *et al*: The inositol polyphosphate 5-phosphatase PIPP regulates AKT1-dependent breast cancer growth and metastasis. Cancer Cell 28: 155-169, 2015.
43. Sahlberg SH, Spiegelberg D, Glimelius B, Stenerlöw B and Nestor M: Evaluation of cancer stem cell markers CD133, CD44, CD24: Association with AKT isoforms and radiation resistance in colon cancer cells. PLoS One 9: e94621, 2014.
44. Etemadmoghadam D and Bowtell D: AKT1 gene amplification as a biomarker of treatment response in ovarian cancer: Mounting evidence of a therapeutic target. Gynecol Oncol 135: 409-410, 2014.
45. Yu H, Sun J, Jiang S and Xu Y: MicroRNA-490-3p regulates cell proliferation and apoptosis in gastric cancer via direct targeting of AKT1. Exp Ther Med 17: 1330-1336, 2019.
46. Liu F, Hu H, Zhao J, Zhang Z, Ai X, Tang L and Xie L: miR-124-3p acts as a potential marker and suppresses tumor growth in gastric cancer. Biomed Rep 9: 147-155, 2018.
47. Zhu CY, Meng FQ and Liu J: MicroRNA-524-5p suppresses cell proliferation and promotes cell apoptosis in gastric cancer by regulating CASP3. Eur Rev Med Pharmacol Sci 23: 7968-7977, 2019.
48. Zhao M, Liu Q, Liu W, Zhou H, Zang X and Lu J: MicroRNA-140 suppresses *Helicobacter pylori*-positive gastric cancer growth by enhancing the antitumor immune response. Mol Med Rep 20: 2484-2492, 2019.
49. Geng Y, Lu X, Wu X, Xue L, Wang X and Xu J: MicroRNA-27b suppresses *Helicobacter pylori*-induced gastric tumorigenesis through negatively regulating Frizzled7. Oncol Rep 35: 2441-2450, 2016.
50. Zhou X, Xia Y, Li L and Zhang G: miR-101 inhibits cell growth and tumorigenesis of *Helicobacter pylori* related gastric cancer by repression of SOCS2. Cancer Biol Ther 15: 160-169, 2015.
51. Feng Y, Wang L, Zeng J, Shen L, Liang X, Yu H, Liu S, Liu Z, Sun Y, Li W, *et al*: FoxM1 is overexpressed in *Helicobacter pylori*-induced gastric carcinogenesis and is negatively regulated by miR-370. Mol Cancer Res 11: 834-844, 2013.
52. Yang L, Li C and Jia Y: MicroRNA-99b promotes *Helicobacter pylori*-induced autophagyand suppresses carcinogenesis by targeting mTOR. Oncol Lett 16: 5355-5360, 2018.
53. Liu S, Tian Y, Zhu C, Yang X and Sun Q: High miR-718 suppresses phosphatase and tensin homolog (PTEN) expression and correlates to unfavorable prognosis in gastric cancer. Med Sci Monit 24: 5840-5850, 2018.
54. Wang Q, He Y, Kan W, Li F, Ji X, Wu X, Wang X, Zhang Y and Chen J: microRNA-32-5p targets KLF2 to promote gastric cancer by activating PI3K/AKT signaling pathway. Am J Transl Res 11: 4895-4908, 2019.
55. Zhou H, Liu H, Jiang M, Zhang S, Chen J and Fan X: Targeting MicroRNA-21 suppresses gastric cancer cell proliferation and migration via PTEN/Akt signaling axis. Cell Transplant 28: 306-317, 2019.
56. Wei S, Peng L, Yang J, Sang H, Jin D, Li X, Chen M, Zhang W, Dang Y and Zhang G: Exosomal transfer of miR-15b-3p enhances tumorigenesis and malignant transformation through the DYNLT1/Caspase-3/Caspase-9 signaling pathway in gastric cancer. J Exp Clin Cancer Res 39: 32, 2020.
57. Huang J, Shen M, Yan M, Cui Y, Gao Z and Meng X: Exosome-mediated transfer of miR-1290 promotes cell proliferation and invasion in gastric cancer via NKD1. Acta Biochim Biophys Sin (Shanghai) 51: 900-907, 2019.
58. Angonin D and Van Raay TJ: Nkd1 functions as a passive antagonist of Wnt signaling. PLoS One 8: e74666, 2013.
59. Yan D, Wallingford JB, Sun TQ, Nelson AM, Sakanaka C, Reinhard C, Harland RM, Fantl WJ and Williams LT: Cell autonomous regulation of multiple dishevelled-dependent pathways by mammalian Nkd. Proc Natl Acad Sci USA 98: 3802-3807, 2001.
60. Wharton KA Jr, Zimmermann G, Rousset R and Scott MP: Vertebrate proteins related to drosophila naked cuticle bind dishevelled and antagonize Wnt signaling. Dev Biol 234: 93-106, 2001.
61. Zhu Y, Jiang Q, Lou X, Ji X, Wen Z, Wu J, Tao H, Jiang T, He W, Wang C, *et al*: MicroRNAs up-regulated by CagA of *Helicobacter pylori* induce intestinal metaplasia of gastric epithelial cells. PLoS One 7: e35147, 2012.
62. Shen E, Wang X, Liu X, Lv M, Zhang L, Zhu G and Sun Z: MicroRNA-93-5p promotes epithelial-mesenchymal transition in gastric cancer by repressing tumor suppressor AHNAK expression. Cancer Cell Int 20: 76, 2020.
63. Nagl NG Jr, Patsialou A, Haines DS, Dallas PB, Beck GR Jr and Moran E: The p270 (ARID1A/SMARCF1) subunit of mammalian SWI/SNF-related complexes is essential for normal cell cycle arrest. Cancer Res 65: 9236-9244, 2005.
64. Shigetomi H, Oonogi A, Tsunemi T, Tanase Y, Yamada Y, Kajihara H, Yoshizawa Y, Furukawa N, Haruta S, Yoshida S, *et al*: The role of components of the chromatin modification machinery in carcinogenesis of clear cell carcinoma of the ovary (Review). Oncol Lett 2: 591-597, 2011.
65. Cheng S, Wang L, Deng CH, Du SC and Han ZG: ARID1A represses hepatocellular carcinoma cell proliferation and migration through lncRNA MVIH. Biochem Biophys Res Commun 491: 178-182, 2017.
66. Zhu Y, Li K, Yan L, He Y, Wang L and Sheng L: miR-223-3p promotes cell proliferation and invasion by targeting Arid1a in gastric cancer. Acta Biochim Biophys Sin (Shanghai) 52: 150-159, 2020.
67. Yang Y, Yin ZX, Wang ZY, Tian SB, Wang HC, Zhang FX, Li LP, Zheng C and Kong S: miR-7641 depletion suppresses proliferation of gastric cancer cells by targeting ARID1A. Anticancer Drugs 31: 368-376, 2020.
68. Zhang X, Zhang M, Wang G, Tian Y and He X: Tumor promoter role of miR-647 in gastric cancer via repression of TP73. Mol Med Rep 18: 3744-3750, 2018.
69. Yang F, Xu Y, Liu C, Ma C, Zou S, Xu X, Jia J and Liu Z: NF-κB/miR-223-3p/ARID1A axis is involved in *Helicobacter pylori* CagA-induced gastric carcinogenesis and progression. Cell Death Dis 9: 12, 2018.
70. Cui HB, Ge HE, Wang YS and Bai XY: miR-208a enhances cell proliferation and invasion of gastric cancer by targeting SFRP1 and negatively regulating MEG3. Int J Biochem Cell Biol 102: 31-39, 2018.
71. Lin J, Shen J, Yue H and Cao Z: miRNA-183-5p.1 promotes the migration and invasion of gastric cancer AGS cells by targeting TPM1. Oncol Rep 42: 2371-2381, 2019.
72. Pelengaris S and Khan M: The many faces of c-MYC. Arch Biochem Biophys 416: 129-136, 2003.
73. Deng T, Zhang H, Yang H, Wang H, Bai M, Sun W, Wang X, Si Y, Ning T, Zhang L, *et al*: Exosome miR-155 derived from gastric carcinoma promotes angiogenesis by targeting the c-MYB/VEGF axis of endothelial cells. Mol Ther Nucleic Acids 19: 1449-1459, 2020.
74. Maiese K, Hou J, Chong ZZ and Shang YC: A fork in the path: Developing therapeutic inroads with FoxO proteins. Oxid Med Cell Longev 2: 119-129, 2009.
75. Zhou Z, Zhang H, Deng T, Ning T, Liu R, Liu D, Bai M, Ying G and Ba Y: Exosomes carrying MicroRNA-155 target forkhead box O3 of endothelial cells and promote angiogenesis in gastric cancer. Mol Ther Oncolytics 15: 223-233, 2019.
76. Yang H, Zhang H, Ge S, Ning T, Bai M, Li J, Li S, Sun W, Deng T, Zhang L, *et al*: Exosome-derived miR-130a activates angiogenesis in gastric cancer by targeting C-MYB in vascular endothelial cells. Mol Ther 26: 2466-2475, 2018.
77. Shi Y, Yang Z, Zhang T, Shen L, Li Y and Ding S: SIRT1-targeted miR-543 autophagy inhibition and epithelial-mesenchymal transition promotion in *Helicobacter pylori* CagA-associated gastric cancer. Cell Death Dis 10: 625, 2019.
78. Tan X, Tang H, Bi J, Li N and Jia Y: MicroRNA-222-3p associated with *Helicobacter pylori* targets HIPK2 to promote cell proliferation, invasion, and inhibits apoptosis in gastric cancer. J Cell Biochem 119: 5153-5162, 2018.
79. Cheng Y, Jia B, Wang Y and Wan S: miR-133b acts as a tumor suppressor and negatively regulates ATP citrate lyase via PPARγ in gastric cancer. Oncol Rep 38: 3220-3226, 2017.
80. Cai H, Lin H, Cao W, Sun J, Huang Y and Fang Y: Downregulation of miR-519a predicts poor prognosis and contributes to tumor progression in gastric cancer. Oncol Res Treat 43: 19-26, 2020.
81. Lv H, Hou H, Lei H, Nie C, Chen B, Bie L, Han L and Chen X: MicroRNA-6884-5p regulates the proliferation, invasion and EMT of gastric cancer cells by directly targeting S100A16. Oncol Res 28: 225-236, 2020.
82. Chen XB, Li W and Chu AX: MicroRNA-133a inhibits gastric cancer cells growth, migration, and epithelial-mesenchymal transition process by targeting presenilin 1. J Cell Biochem 120: 470-480, 2019.
83. Yu H, Zhang J, Wen Q, Dai Y, Zhang W, Li F and Li J: MicroRNA-6852 suppresses cell proliferation and invasion via targeting forkhead box J1 in gastric cancer. Exp Ther Med 16: 3249-3255, 2018.

84. Ouyang Y, Yuan W and Qiu S: MicroRNA-153 functions as a tumor suppressor in gastric cancer via targeting Kruppel-like factor 5. Exp Ther Med 16: 473-482, 2018.

85. Jia C, Zhang Y, Xie Y, Ren Y, Zhang H, Zhou Y, Gao N, Ding S and Han S: miR-200a-3p plays tumor suppressor roles in gastric cancer cells by targeting KLF12. Artif Cells Nanomed Biotechnol 47: 3697-3703, 2019.

86. Su H, Ren F, Jiang H, Chen Y and Fan X: Upregulation of microRNA-520a-3p inhibits the proliferation, migration and invasion via spindle and kinetochore associated 2 in gastric cancer. Oncol Lett 18: 3323-3330, 2019.

87. Song Z, Li W, Wang L, Jia N and Chen B: MicroRNA-454 inhibits tumor cell proliferation, migration and invasion by downregulating zinc finger E-box-binding homeobox 1 in gastric cancer. Mol Med Rep 16: 9067-9073, 2017.

88. Zhang J, Wang C, Yan S, Yang Y, Zhang X and Guo W: miR-345 inhibits migration and stem-like cell phenotype in gastric cancer via inactivation of Rac1 by targeting EPS8. Acta Biochim Biophys Sin (Shanghai) 52: 259-267, 2020.

89. Wang J, Feng W, Dong Y, Mao X, Guo F and Luo F: MicroRNA-495 regulates human gastric cancer cell apoptosis and migration through Akt and mTOR signaling. Oncol Rep 40: 3654-3662, 2018.

90. Yuan KT, Li BX, Yuan YJ, Tan M, Tan JF, Dai WG, Feng WD and Zuo JD: Deregulation of MicroRNA-375 inhibits proliferation and migration in gastric cancer in association with autophagy-mediated AKT/mTOR signaling pathways. Technol Cancer Res Treat 17: 1533033818806499, 2018.

91. Miao L, Liu K, Xie M, Xing Y and Xi T: miR-375 inhibits *Helicobacter pylori*-induced gastric carcinogenesis by blocking JAK2-STAT3 signaling. Cancer Immunol Immunother 63: 699-711, 2014.

92. Xu XC, Zhang WB, Li CX, Gao H, Pei Q, Cao BW and He TH: Up-regulation of miR-1915 inhibits proliferation, invasion, and migration of *Helicobacter pylori*-infected gastric cancer cells via targeting RAGE. Yonsei Med J 60: 38-47, 2019.

93. Zhang S, Zhang R, Xu R, Shang J, He H and Yang Q: MicroRNA-574-5p in gastric cancer cells promotes angiogenesis by targeting protein tyrosine phosphatase non-receptor type 3 (PTPN3). Gene 733: 144383, 2020.

94. Li Q, Li B, Li Q, Wei S, He Z, Huang X, Wang L, Xia Y, Xu Z, Li Z, *et al*: Exosomal miR-21-5p derived from gastric cancer promotes peritoneal metastasis via mesothelial-to-mesenchymal transition. Cell Death Dis 9: 854, 2018.

95. Feng C, She J, Chen X, Zhang Q, Zhang X, Wang Y, Ye J, Shi J, Tao J, Feng M, *et al*: Exosomal miR-196a-1 promotes gastric cancer cell invasion and metastasis by targeting SFRP1. Nanomedicine (Lond) 14: 2579-2593, 2019.

96. Zhang X, Peng Y, Huang Y, Deng S, Feng X, Hou G, Lin H, Wang J, Yan R, Zhao Y, *et al*: Inhibition of the miR-192/215-Rab11-FIP2 axis suppresses human gastric cancer progression. Cell Death Dis 9: 778, 2018.

97. Sun F, Ni Y, Zhu H, Fang J, Wang H, Xia J, Ding F, Shen H and Shao S: microRNA-29a-3p, Up-regulated in human gastric cells and tissues with *H. Pylori* infection, promotes the migration of GES-1 cells via A20-mediated EMT pathway. Cell Physiol Biochem 51: 1250-1263, 2018.

98. Zhang Q, Sui Y and Sui X: MicroRNA-761 inhibits the metastasis of gastric cancer by negatively regulating Ras and Rab interactor 1. Oncol Lett 18: 3097-3103, 2019.

99. Xiao F, Cheng Z, Wang P, Gong B, Huang H, Xing Y and Liu F: MicroRNA-28-5p inhibits the migration and invasion of gastric cancer cells by suppressing AKT phosphorylation. Oncol Lett 15: 9777-9785, 2018.

100. Bassères DS, Tizzei EV, Duarte AA, Costa FF and Saad ST: ARHGAP10, a novel human gene coding for a potentially cytoskeletal Rho-GTPase activating protein. Biochem Biophys Res Commun 294: 579-585, 2002.

101. Wang Z, Yao L, Li Y, Hao B, Wang M, Wang J, Gu W, Zhan H, Liu G and Wu Q: miR-337-3p inhibits gastric tumor metastasis by targeting ARHGAP10. Mol Med Rep 21: 705-719, 2020.

102. Clem BF, O'Neal J, Tapolsky G, Clem AL, Imbert-Fernandez Y, Kerr DA II, Klarer AC, Redman R, Miller DM, Trent JO, *et al*: Targeting 6-phosphofructo-2-kinase (PFKFB3) as a therapeutic strategy against cancer. Mol Cancer Ther 12: 1461-1470, 2013.

103. Imbert-Fernandez Y, Clem A, Clem B, Tapolsky G, Telang S and Chesney J: Suppression of 6-phosphofructo-2-kinase (PFKFB3) for the treatment of breast cancer. Cancer Res 76 (14 Suppl): S56, 2016.

104. Chen X, Wang A and Yue X: miR-449c inhibits migration and invasion of gastric cancer cells by targeting PFKFB3. Oncol Lett 16: 417-424, 2018.

105. Xiao WS, Li DF, Tang YP, Chen YZ, Deng WB, Chen J, Zhou WW and Liao AJ: Inhibition of epithelial-mesenchymal transition in gastric cancer cells by miR-711-mediated downregulation of CD44 expression. Oncol Rep 40: 2844-2853, 2018.

106. Li J, Zhang B, Cui J, Liang Z and Liu K: miR-203 inhibits the invasion and EMT of gastric cancer cells by directly targeting annexin A4. Oncol Res 27: 789-799, 2019.

107. Zhou X, Xu G, Yin C, Jin W and Zhang G: Down-regulation of miR-203 induced by *Helicobacter pylori* infection promotes the proliferation and invasion of gastric cancer by targeting CASK. Oncotarget 5: 11631-11640, 2014.

108. Chen G, Yang Z, Feng M and Wang Z: microRNA-217 suppressed epithelial-to-mesenchymal transition through targeting PTPN14 in gastric cancer. Biosci Rep 40: BSR20193176, 2020.

109. Zhang M, Huang S and Long D: miR-381 inhibits migration and invasion in human gastric carcinoma through downregulatedting SOX4. Oncol Lett 14: 3760-3766, 2017.

110. Wang F, Liu J, Zou Y, Jiao Y, Huang Y, Fan L, Li X, Yu H, He C, Wei W, *et al*: MicroRNA-143-3p, up-regulated in *H. pylori*-positive gastric cancer, suppresses tumor growth, migration and invasion by directly targeting AKT2. Oncotarget 8: 28711-28724, 2017.

111. Liu X, Ji Q, Zhang C, Liu X, Liu Y, Liu N, Sui H, Zhou L, Wang S and Li Q: miR-30a acts as a tumor suppressor by double-targeting COX-2 and BCL9 in *H. pylori* gastric cancer models. Sci Rep 7: 7113, 2017.

112. Emami SS, Nekouian R, Akbari A, Faraji A, Abbasi V and Agah S: Evaluation of circulating miR-21 and miR-222 as diagnostic biomarkers for gastric cancer. J Cancer Res Ther 15: 115-119, 2019.

113. Saito R, Maruyama S, Kawaguchi Y, Akaike H, Shimizu H, Furuya S, Kawaida H and Ichikawa D: miR-99a-5p as possible diagnostic and prognostic marker in patients with gastric cancer. J Surg Res 250: 193-199, 2020.

114. ZiaSarabi P, Sorayayi S, Hesari A and Ghasemi F: Circulating microRNA-133, microRNA-17 and microRNA-25 in serum and its potential diagnostic value in gastric cancer. J Cell Biochem 120: 12376-12381, 2019.

115. Ji B, Huang Y, Gu T, Zhang L, Li G and Zhang C: Potential diagnostic and prognostic value of plasma long noncoding RNA LINC00086 and miR-214 expression in gastric cancer. Cancer Biomark 24: 249-255, 2019.

116. Yun J, Han SB, Kim HJ, Go SI, Lee WS, Bae WK, Cho SH, Song EK, Lee OJ, Kim HK, *et al*: Exosomal miR-181b-5p downregulation in ascites serves as a potential diagnostic biomarker for gastric cancer-associated malignant ascites. J Gastric Cancer 19: 301-314, 2019.

117. Jiang X, Jiang M, Xu M, Xu J and Li Y: Identification of diagnostic utility and molecular mechanisms of circulating miR-551b-5p in gastric cancer. Pathol Res Pract 215: 900-904, 2019.

118. Li Y, Sun H, Guan J, Ji T and Wang X: Serum microRNA-381: A potential marker for early diagnosis of gastric cancer. Yonsei Med J 60: 720-726, 2019.

119. Xu YC, Liu X, Li M, Li Y, Li CY, Lu Y, Sanches J, Wang L, Du Y, Mao LM, *et al*: A novel mechanism of doxorubicin resistance and tumorigenesis mediated by MicroRNA-501-5p-suppressed BLID. Mol Ther Nucleic Acids 12: 578-590, 2018.

120. Wu DM, Hong XW, Wang LL, Cui XF, Lu J, Chen GQ and Zheng YL: MicroRNA-17 inhibition overcomes chemoresistance and suppresses epithelial-mesenchymal transition through a DEDD-dependent mechanism in gastric cancer. Int J Biochem Cell Biol 102: 59-70, 2018.

121. Zhang H, Deng T, Liu R, Ning T, Yang H, Liu D, Zhang Q, Lin D, Ge S, Bai M, *et al*: CAF secreted miR-522 suppresses ferroptosis and promotes acquired chemo-resistance in gastric cancer. Mol Cancer 19: 43, 2020.

122. Wang Z, Cai Q, Jiang Z, Liu B, Zhu Z and Li C: Prognostic role of microRNA-21 in gastric cancer: A meta-analysis. Med Sci Monit 20: 1668-1674, 2014.

123. Zhang BG, Li JF, Yu BQ, Zhu ZG, Liu BY and Yan M: microRNA-21 promotes tumor proliferation and invasion in gastric cancer by targeting PTEN. Oncol Rep 27: 1019-1026, 2012.

124. Roy S, Yu Y, Padhye SB, Sarkar FH and Majumdar AP: Difluorinated-curcumin (CDF) restores PTEN expression in colon cancer cells by down-regulating miR-21. PLoS One 8: e68543, 2013.

125. Qiang Z, Meng L, Yi C, Yu L, Chen W and Sha W: Curcumin regulates the miR-21/PTEN/Akt pathway and acts in synergy with PD98059 to induce apoptosis of human gastric cancer MGC-803 cells. J Int Med Res 47: 1288-1297, 2019.

126. Yan R, Li K, Yuan DW, Wang HN, Zhang Y, Dang CX and Zhu K: Downregulation of microRNA-4295 enhances cisplatin-induced gastric cancer cell apoptosis through the EGFR/PI3K/Akt signaling pathway by targeting LRIG1. Int J Oncol 53: 2566-2578, 2018.

127. Lang C, Xu M, Zhao Z, Chen J and Zhang L: MicroRNA-96 expression induced by low-dose cisplatin or doxorubicin regulates chemosensitivity, cell death and proliferation in gastric cancer SGC7901 cells by targeting FOXO1. Oncol Lett 16: 4020-4026, 2018.

128. Guo W, Li W, Yuan L, Mei X and Hu W: MicroRNA-106a-3p induces apatinib resistance and activates janus-activated kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) by targeting the SOCS system in gastric cancer. Med Sci Monit 25: 10122-10128, 2019.

129. Shao L, Chen Z, Soutto M, Zhu S, Lu H, Romero-Gallo J, Peek R, Zhang S and El-Rifai W: *Helicobacter pylori*-induced miR-135b-5p promotes cisplatin resistance in gastric cancer. FASEB J 33: 264-274, 2019.

130. Tang S, Fu H, Xu Q and Zhou Y: miR-20a regulates sensitivity of colorectal cancer cells to NK cells by targeting MICA. Biosci Rep 39: BSR20180695, 2019.

131. Shekari N, Javadian M, Ghaffari S, Baradaran B, Darabi M and Kazemi T: DHA abolishes the detrimental effect of docetaxel on downregulation of the MICA via decreasing the expression level of MicroRNA-20a in gastric cancer. J Gastrointest Cancer 51: 545-551, 2020.

132. Zhou X, Su J, Zhu L and Zhang G: *Helicobacter pylori* modulates cisplatin sensitivity in gastric cancer by down-regulating miR-141 expression. Helicobacter 19: 174-181, 2014.

133. Wang M, Qiu R, Yu S, Xu X, Li G, Gu R, Tan C, Zhu W and Shen B: Paclitaxel-resistant gastric cancer MGC-803 cells promote epithelial-to-mesenchymal transition and chemoresistance in paclitaxel-sensitive cells via exosomal delivery of miR155-5p. Int J Oncol 54: 326-338, 2019.

134. Wei X, Gao M, Ahmed Y, Gao M, Liu W, Zhang Y, Xie X, Zhao Q, Wang H and Gu K: MicroRNA-362-5p enhances the cisplatin sensitivity of gastric cancer cells by targeting suppressor of zeste 12 protein. Oncol Lett 18: 1607-1616, 2019.

135. Li M, Gao M, Xie X, Zhang Y, Ning J, Liu P and Gu K: MicroRNA-200c reverses drug resistance of human gastric cancer cells by targeting regulation of the NER-ERCC3/4 pathway. Oncol Lett 18: 145-152, 2019.

136. Sui H, Lou A, Li Z and Yang J: Lidocaine inhibits growth, migration and invasion of gastric carcinoma cells by up-regulation of miR-145. BMC Cancer 19: 233, 2019.

137. Peng C, Huang K, Liu G, Li Y and Yu C: miR-876-3p regulates cisplatin resistance and stem cell-like properties of gastric cancer cells by targeting TMED3. J Gastroenterol Hepatol 34: 1711-1719, 2019.

138. Kang DW, Yang ES, Noh YN, Hwang WC, Jo SY, Suh YA, Park WS, Choi KY and Min DS: MicroRNA-320a and microRNA-4496 attenuate *Helicobacter pylori* cytotoxin-associated gene A (CagA)-induced cancer-initiating potential and chemoresistance by targeting β-catenin and ATP-binding cassette, subfamily G, member 2. J Pathol 241: 614-625, 2017.